Axial Spondyloarthritis Imaging for Clinical Trials

Sally Warner PhD and Farhan Syed, PhD

Agenda

- Axial Spondyloarthritis (SpA) overview
- Imaging for Axial SpA
- Imaging Assessment Criteria
- Axial SpA Clinical Trials

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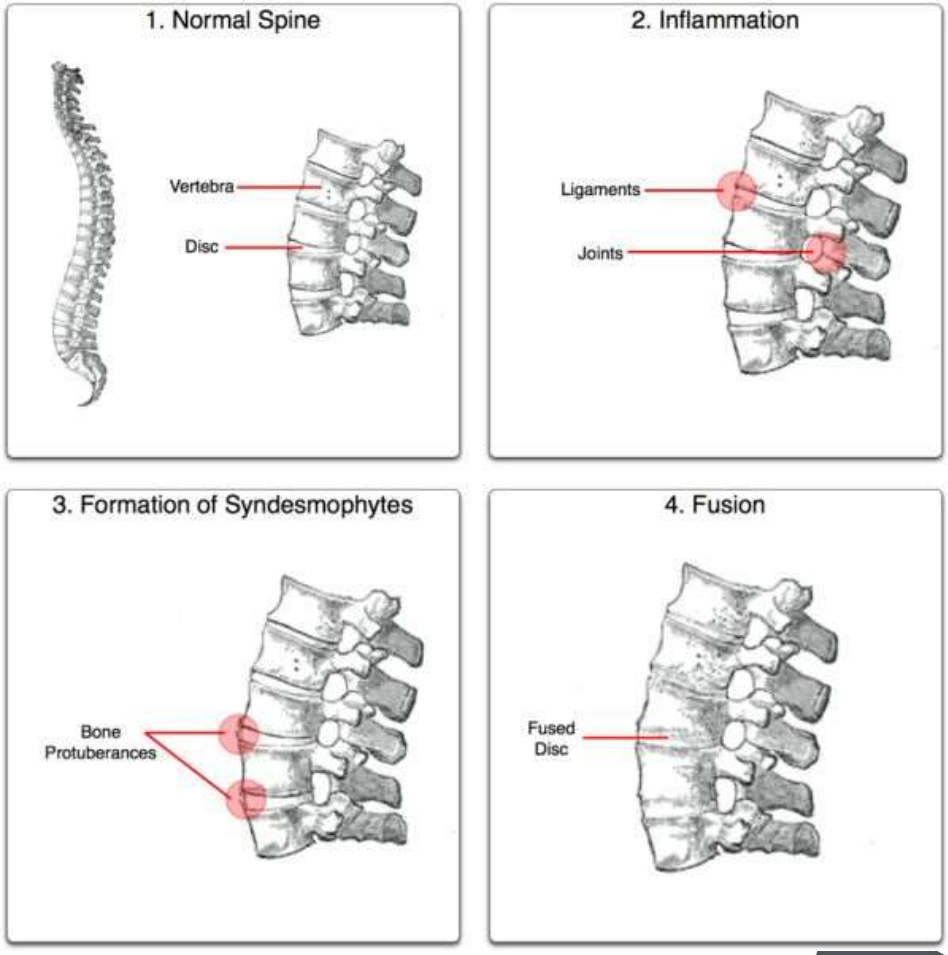
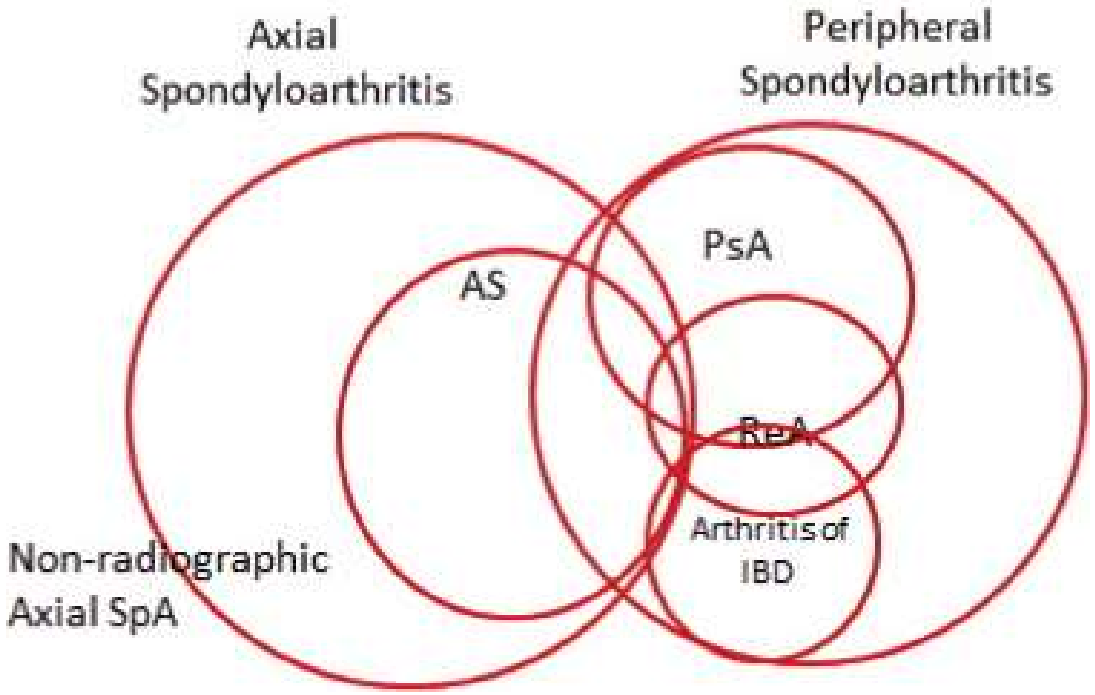
Axial Spondyloarthritis (ax-SpA) overview

Ankylosing Spondylitis Progression



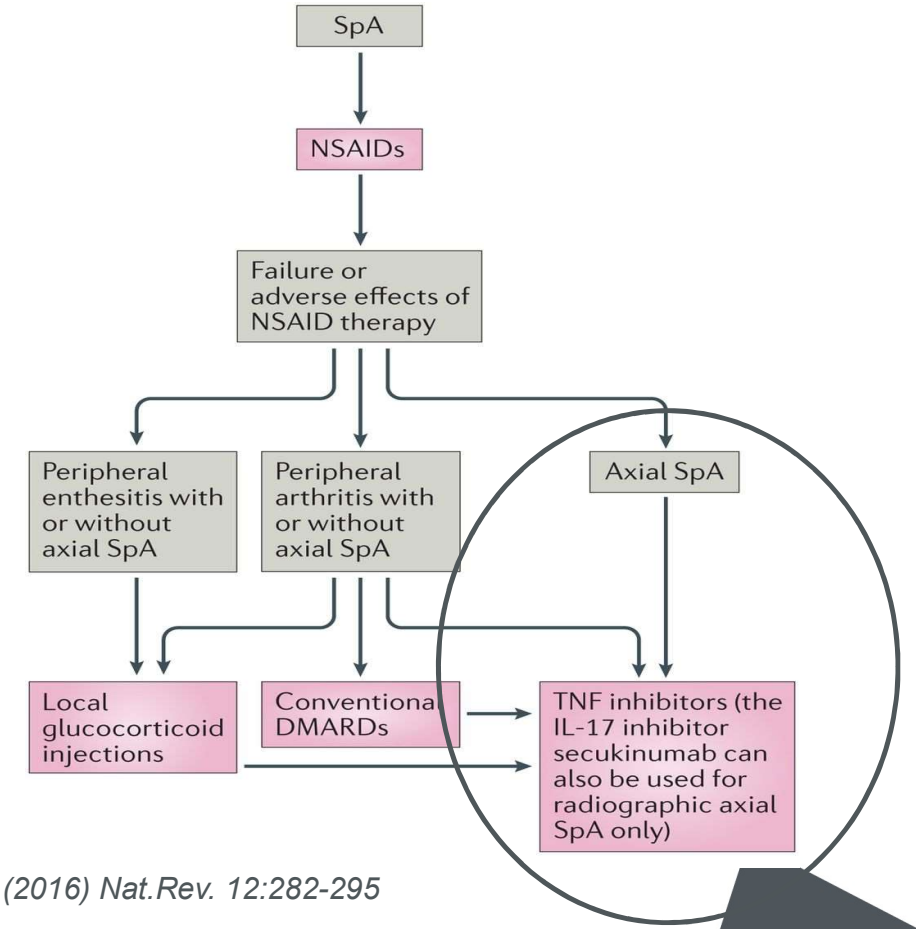
http://en.wikipedia.org/wiki/Image:Ankylosing_process.jpg

Spectrum of Spondyloarthritis: Current concept



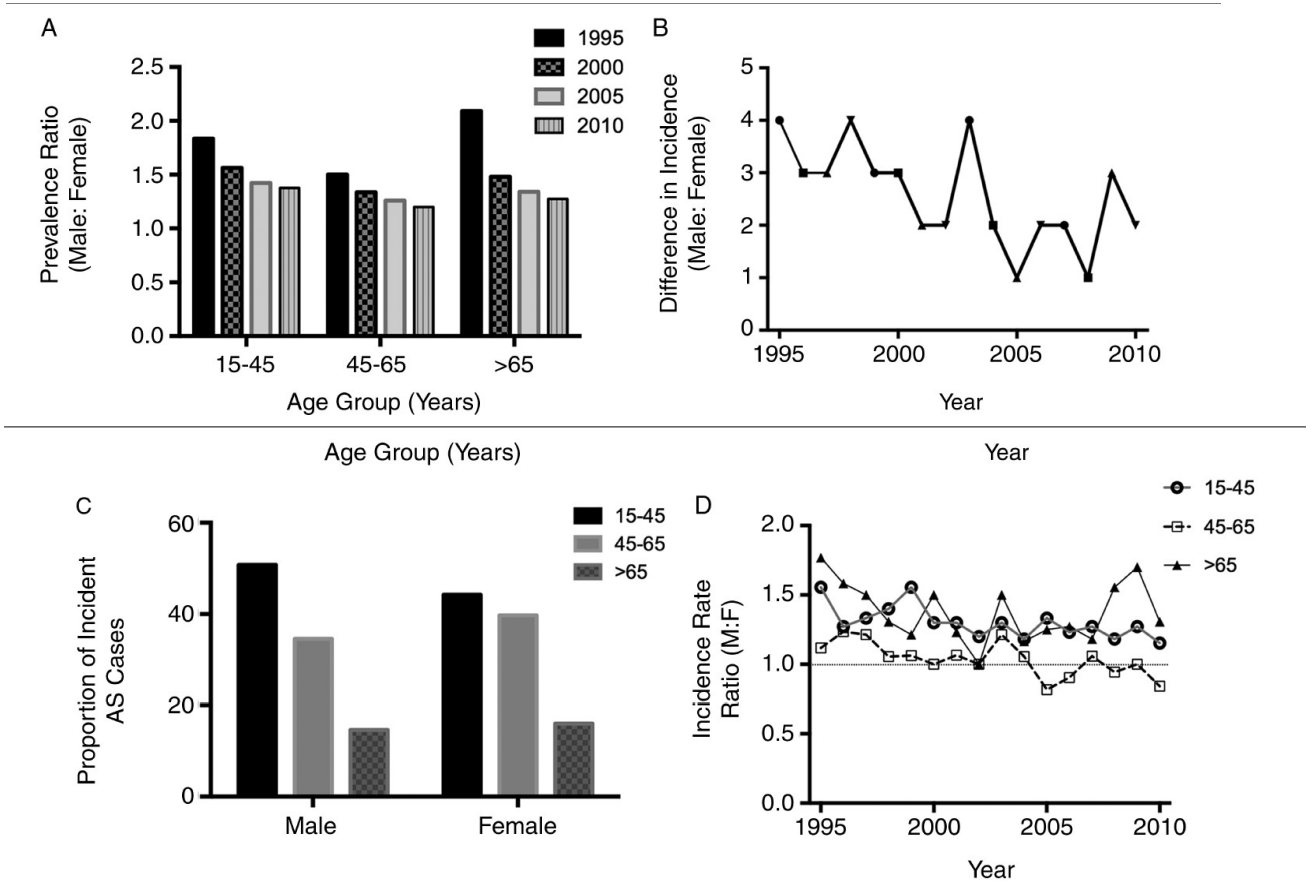
Garg et al (2014); Best Pract. Res. Clin. Rheum. 28(5): 663-672

Treatment strategies for Spondyloarthritis



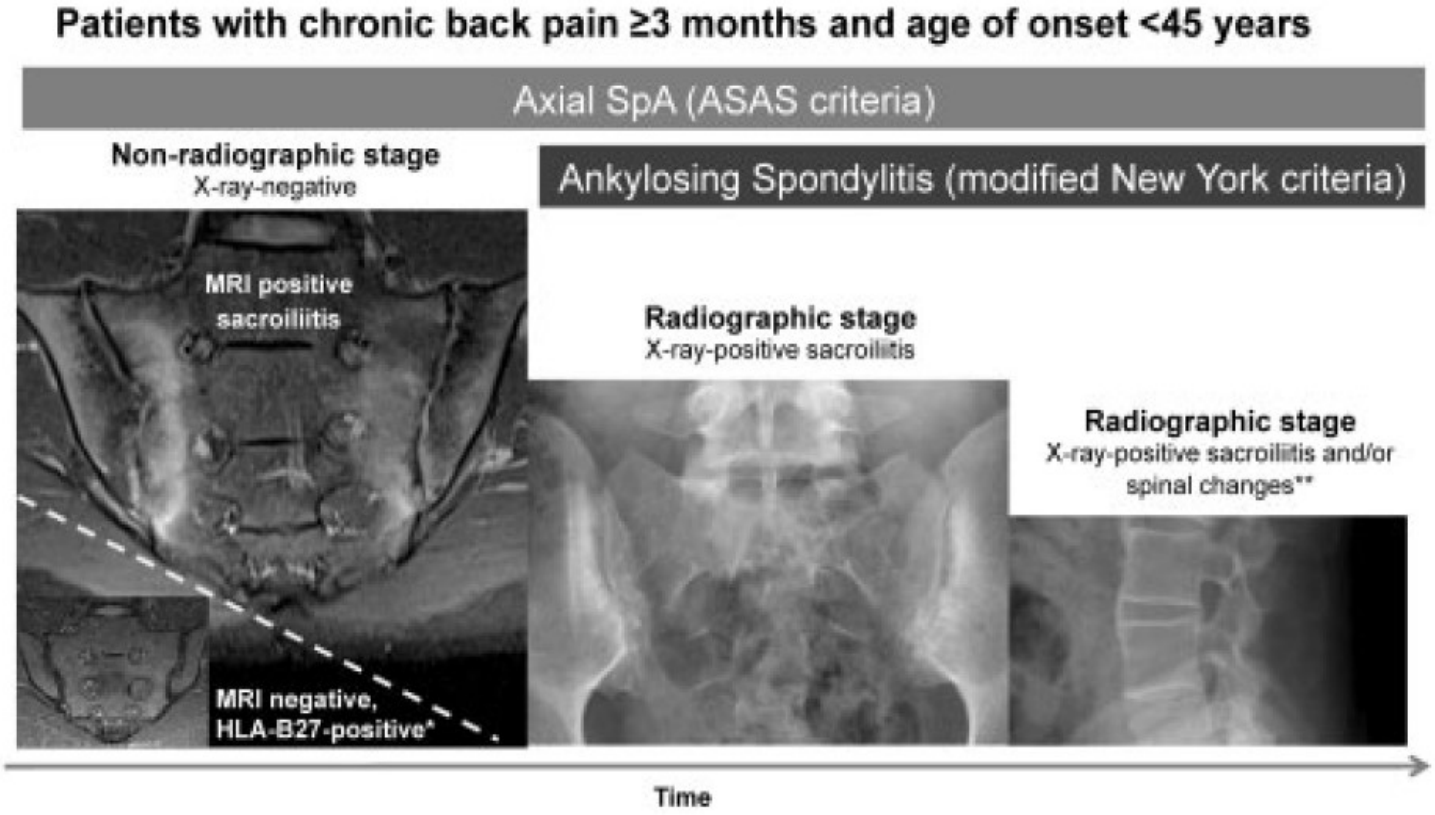
Seiper and Poddubnyy (2016) Nat.Rev. 12:282-295

Prevalence of Axial Spondyloarthritis and gender distribution *(Haroon et al;2014, BMJ Open access)*



Study conducted in Ontario, Canada

Continuous spectrum from non-radiographic axial SpA (nr-axSpA) to the radiographic stage of Ankylosing Spondylitis (AS)



Seiper and van der Heijde (2013), Arth. Rheum. 65(3):543-551

Clinical Trial Protocol Imaging Considerations

- **Imaging Modality?**
  - XR, MRI, CT, PET?
- **Eligibility central review or local review of images?**
  - Single read or Double read with adjudication?
- **Eligibility and Efficacy Imaging Assessments?**
  - Spine and SIJ? Which criteria?
- **Key Opinion Leaders to involve/consult?**
  - Prof. Landewe, Dr. Maksymowych, Dr. Lambert, Prof. Braun, Dr. Baraliakos
- **Population to enroll?**
  - Non-radiographic axial SpA or AS or both?

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Rheumatology Study Challenges

Treatment Effects can be Small and Hard to Demonstrate

- True placebo control not ethical (early escape)
- Comparator group on treatment
- Variability in response

Sources of Variability Must be Minimized

- Imaging harmonized
- Standardized/efficient reading system
- Independent reads by trained experts

Requires Data with Low Variability

Objective:

Increase sensitivity to show treatment effects

High-Quality Images → High-Quality Scoring → High-Quality Results

Imaging Modalities for Axial SpA

Summary Imaging Modalities for Axial-SpA

- XR of SIJ and Spine commonly performed for chronic structural changes
- MRI of SIJ and Spine commonly used for inflammation
- CT of spine and SIJ newer approach for chronic, structural changes
- PET novel, potential use in POC

	SIJ		Spine	
	Eligibility	Efficacy	Eligibility	Efficacy
XR	nr-ax-SpA & AS	AS	AS	AS
MR	nr-axSpA	nr-ax-SpA & AS	-	nr-ax-SpA & AS
CT	-	?	-	AS
PET	?	?	?	?

X-Ray Imaging required

AP Pelvis

Orthogonal to SIJ

Lateral Spine

Cervical:

Bottom 1/3 of C2 through top 1/3 of T1, inclusive

Thoraco-Lumbar:

T10 or T12-S1

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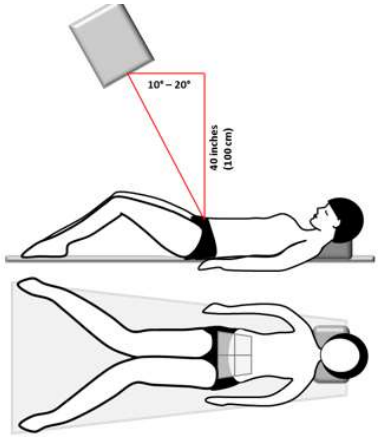
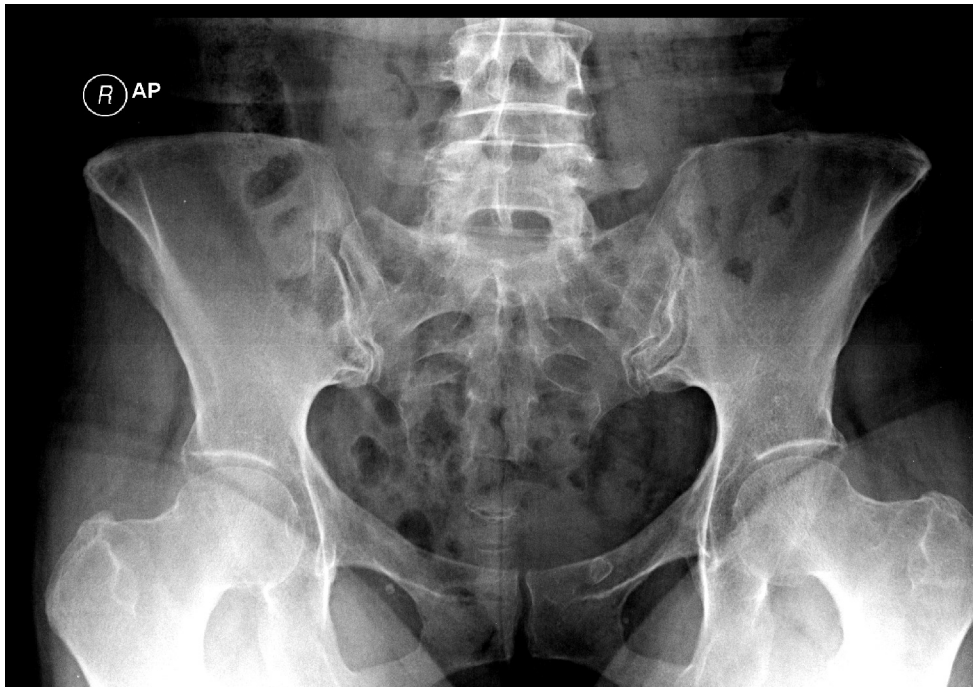
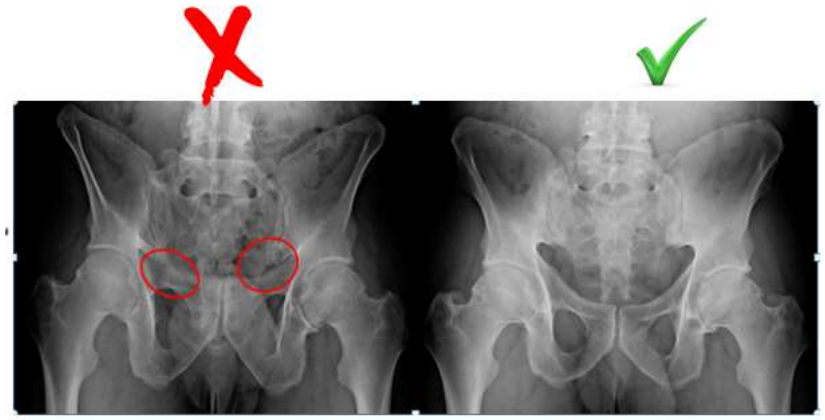
X-Ray Image Quality Challenges

- Be aware of patient positioning and beam angle
- Correct angle of central ray
- Include laterality marker “R” and “AP” in upper right-hand corner of image
- Avoid Artifacts

  NOTE: Excessive gas or excrement in bowels may obscure SIJ(s)

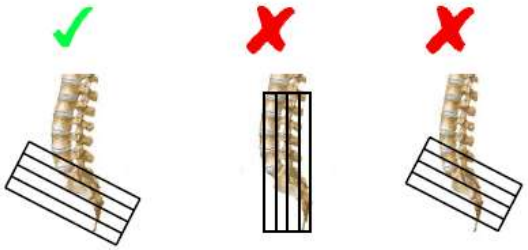




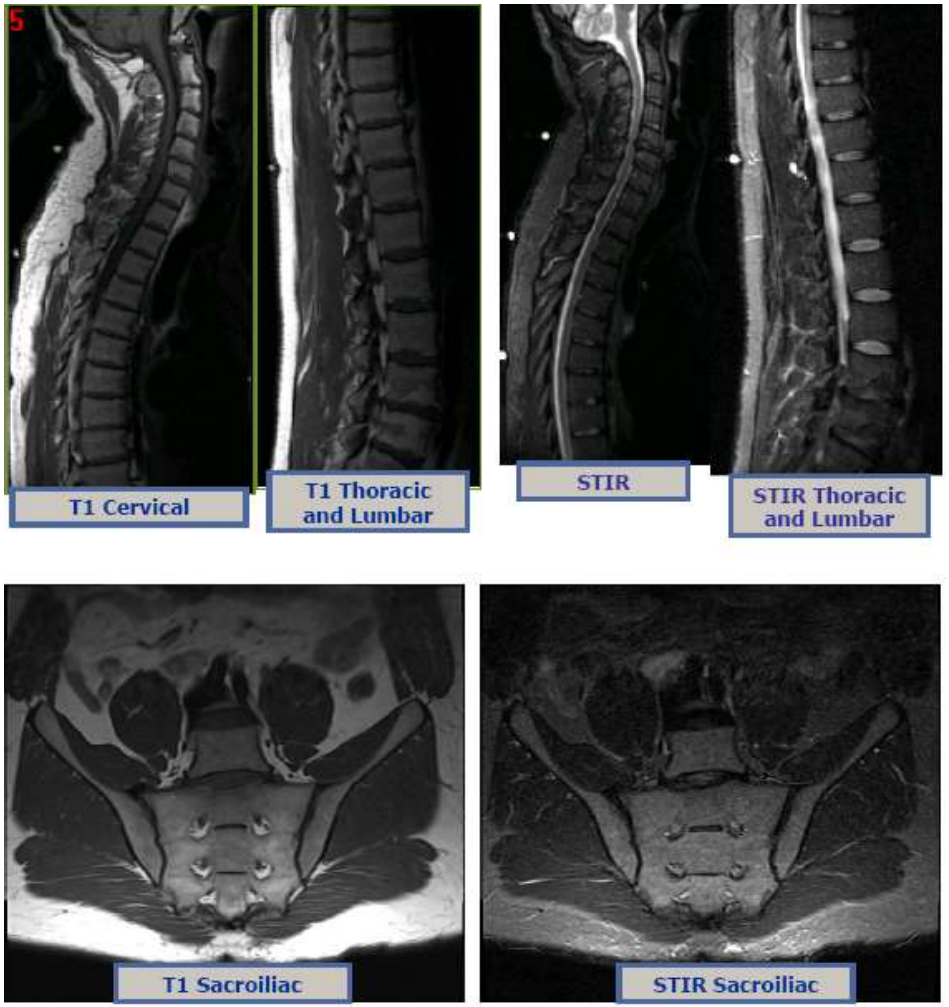


MR Imaging required

- 1.5 T or 3 T magnet
- T1w and STIR
- Sagittal spine
- Oblique coronal SIJ



SPARCC in SIJ requires accurate and consistent slice pick by technologist during acquisition



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STIR MRI Image Quality Challenges

- Perform STIR 1st:
- STIR Sequence Takes Longer than T1
  - Patient Discomfort could cause motion artifact
  - Ensure Consistency of Acquisition Parameters
    - Echo time (TE); Inversion Time (TI);
- Be Aware/Avoid
  - SIJ stack orientation relative to anatomy
  - Artifacts
  - Incomplete anatomical coverage
  - Incomplete or failed fat suppression

Axial SpA Imaging Assessment Criteria

Imaging Assessment Criteria for Axial SpA

- **XR**
  - modified New York criteria (NYmAS)
  - modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)
- **MR**
  - ASAS OMERACT
  - Berlin/ASspiMRI-a, ASspiMRI-c
  - Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Index for Assessment of Spinal Inflammation in Ankylosing Spondylitis (SPARCC)
  - Fat SpA Spine Score (FASSS)
  - MRI SIJ Structural Score (SSS)
- **CT**
  - CT Spine Score (CTSS)

	SIJ		Spine	
	Eligibility	**Efficacy**	**Eligibility**	**Efficacy**
XR	NYmAS	NYmAS	Ankylosis, Syndesmophytes	mSASSS, RASSS
MR	ASAS	SPARCC, Berlin, SSS	-	ASspiMRI, Berlin, SPARCC, FASSS
CT	-	?	-	CTSS

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XR Modified NY SIJ Eligibility criteria for AS studies

SIJ X-Ray < grade 2 bilaterally = NYmAS-

SIJ X-Ray NYmAS > grade 2 bilaterally = NYmAS+ and spine syndesmophyte w/o complete spinal ankylosis

syndesmophyte

Right SIJ Sacroiliitis Grade *	Left SIJ Sacroiliitis Grade *
0	0
1	1
2	2
3	3
4	4
Unable to Evaluate	Unable to Evaluate

0 Normal
1 Suspicious but not definite
2 Minimal: some sclerosis, minimal erosion, no marked joint space narrowing
3 Moderate: definite sclerosis, both sides of the joint with erosions and/or joint space change
4 Ankylosis: complete obliteration of the SI joint with or without sclerosis

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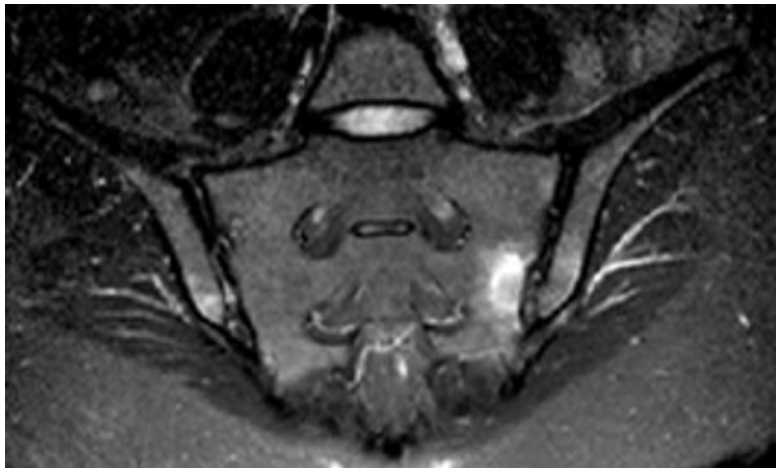
MRI Eligibility Assessment: ASAS / OMERACT

- Presence of Bone Marrow Oedema (BMO) or osteitis that is highly suggestive of spondyloarthritis is required for a positive assessment (MRI+)
- Locations: Subchondral or periarticular bone marrow
- Definition of edema (MRI+): ≥ 1 BMO lesion on one slice or a BMO lesion that is present on ≥ 2 consecutive slices



Lambert RG, et al. Ann Rheum Dis. 2016;75(11):1958-1963.

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XR Spine Efficacy Review Criteria: mSASSS

- Radiograph Assessment Criteria – mSASSS

  The anatomy to be assessed includes:

  - **Cervical Vertebrae:** the lower border of the second cervical vertebra (C2) through the upper border of the first thoracic vertebra (T1).
  - **Lumbar Vertebrae:** the lower border of the twelfth thoracic vertebra (T12), all five lumbar vertebrae (L1-L5), and the upper border of the sacrum (S1).
  - RASSS assessment includes scoring for T10-T12

- Each vertebral site is scored for:
  - 0 = no abnormality
  - 1 = erosion, sclerosis, or squaring
  - 2 = syndesmophyte
  - 3 = total bony bridging at each site
- **Important for readers to clearly see vertebral margins**

Cremers et al. Ann Rheum Dis. 2005 Jan;64(1):127-9.
Baraliakos et al. Arthritis & Rheumatism, 2009, Vol. 61, No. 6: p764–771

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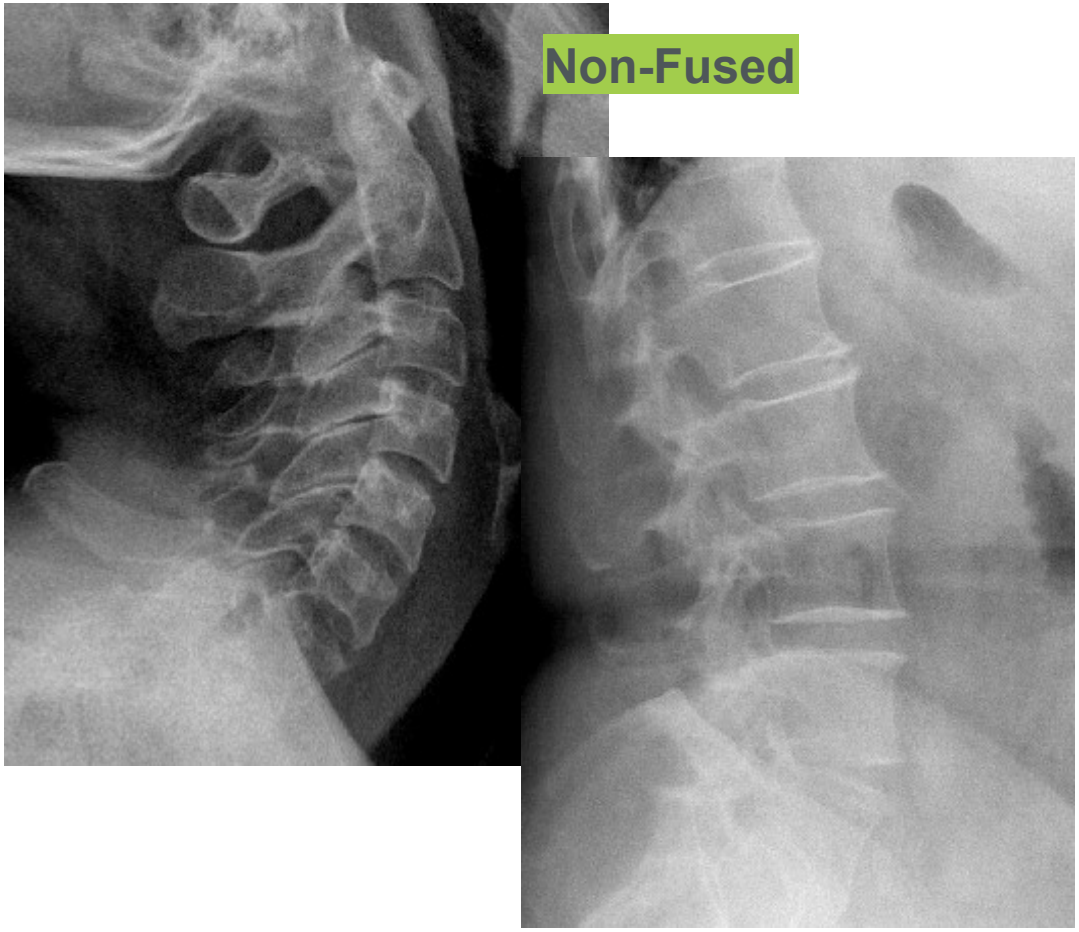
Spine XR Examples

Non-Fused



Total Ankylosis

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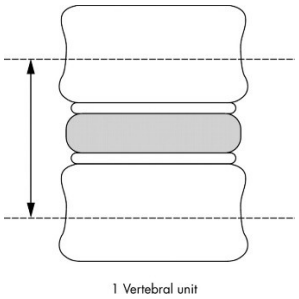
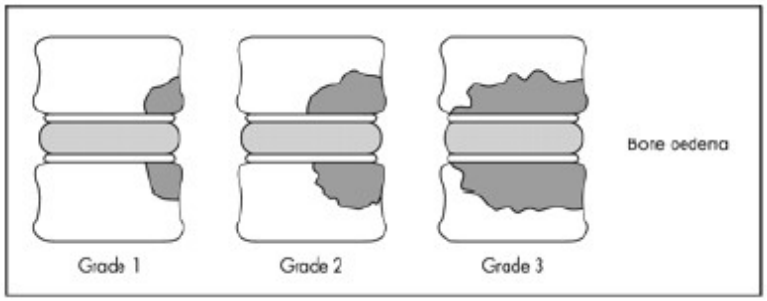
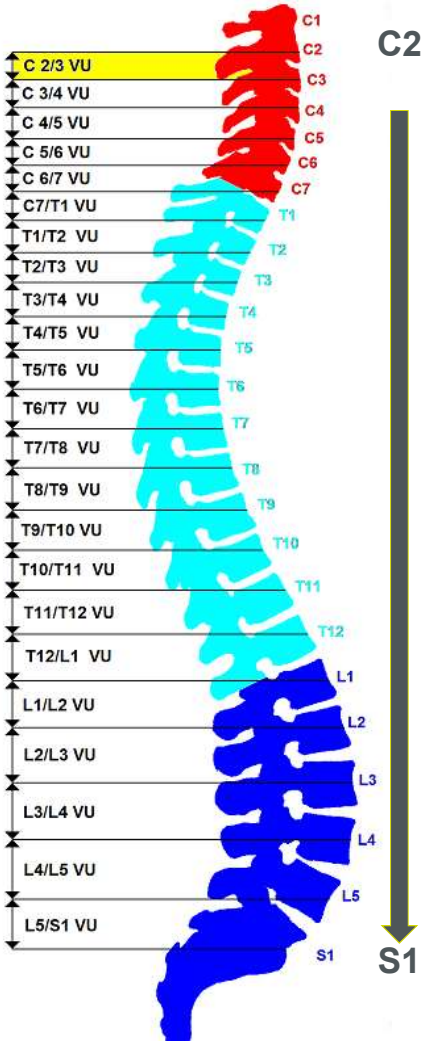
MRI Spine Efficacy Berlin Assessment Criteria

- MRI Assessment Criteria – Berlin (ASspiMRI-a)
  - Assess Spinal Inflammation/Edema – not Erosion (ASspiMRI-c)
  - Requires Sagittal View of Entire Spine
  - Comparison of T1 and STIR Sequences
  - All 23 VU's scored 0-3 for presence and severity of edema



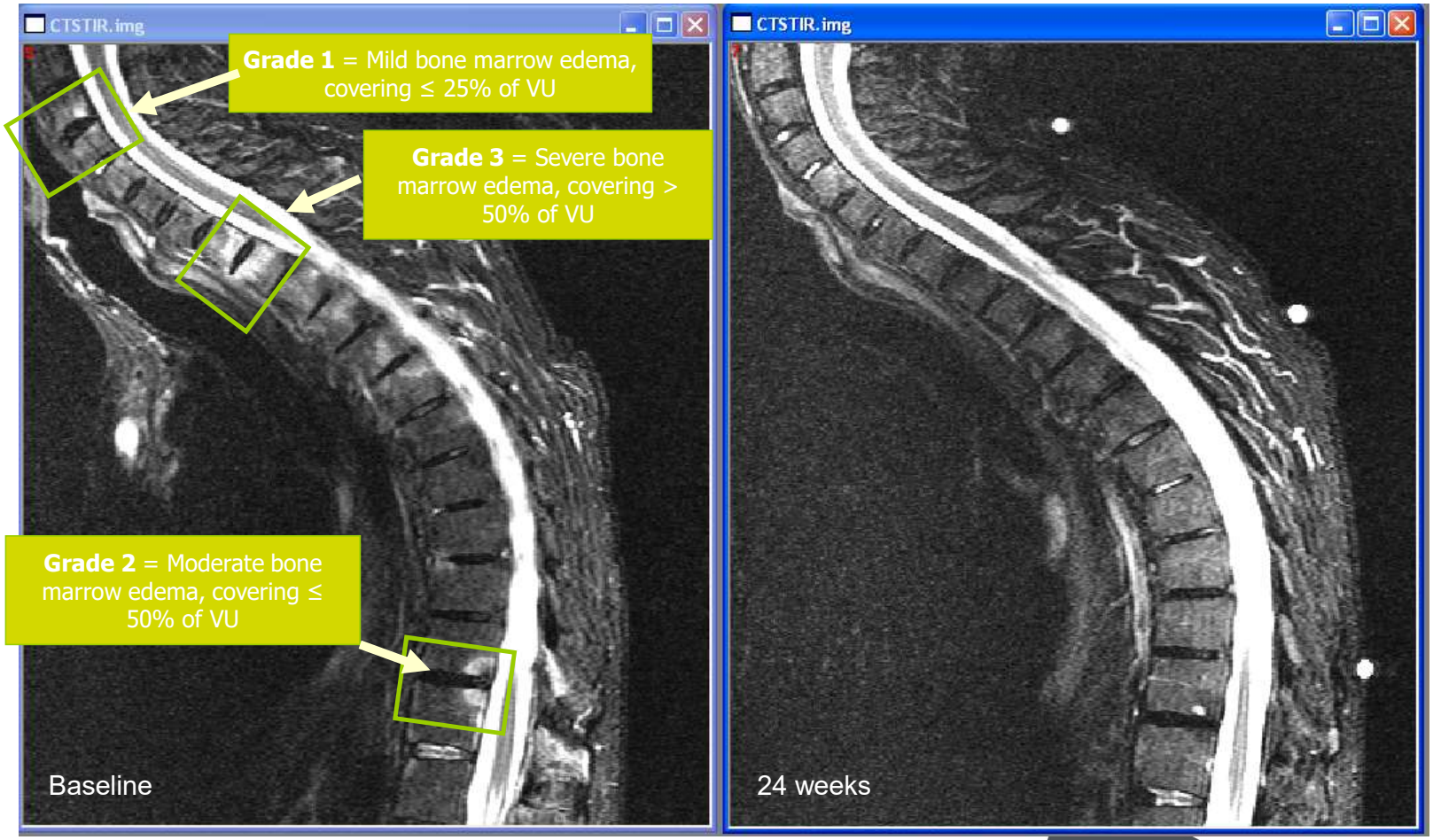


Complete coverage of entire spine is important



- *Braun et al. ARTHRITIS & RHEUMATISM Vol. 48, No. 4, April 2003 pp 1126–1136*

MRI Spine Efficacy Berlin Scoring Example



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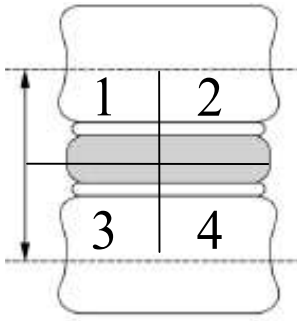
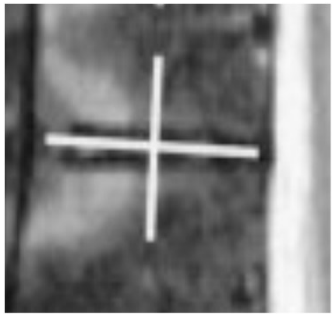
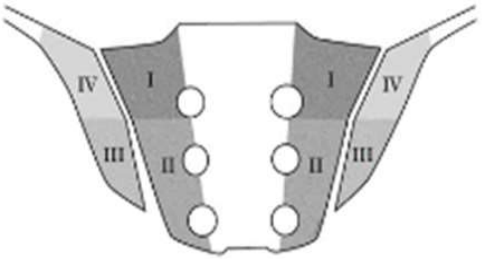
MRI Spine and SIJ Efficacy Review Criteria: SPARCC

- Assessments of edema in spine and SI joint
- Presence, intensity and depth of edema scored in:
  - 6 most affected discovertebral units DVUs of the spine (3 slices) scored 0-1 per quadrant
  - 6 consecutive SIJ slices in all 8 quadrants (I-IV)







THE SPONDYLOARTHRITIS RESEARCH CONSORTIUM OF CANADA

Maksymowych et al. A&R 2007, pp 501–507

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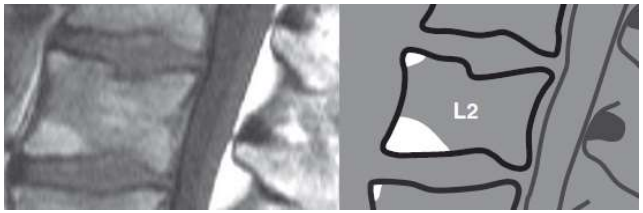
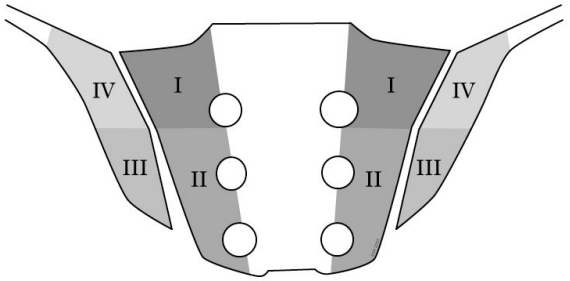
MRI Fatty Lesions and Structural changes

- More recent MRI criteria for assessing SIJ structural progression
- **Consortium of Canada MRI SIJ Structural Score (SSS)**
  - *Maksymowych, W.P., et al., J.Rheum. 2015; 42:79-86*
  - Fat metaplasia & Erosions scored 0-1 per SIJ quadrant on 5 slices
  - Backfill & Ankylosis scored 0-1 per SIJ (L and R) on 5 slices

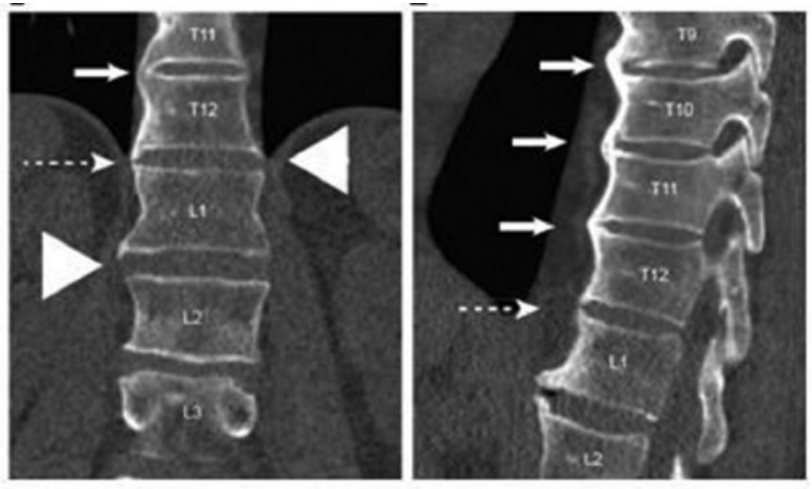


- **Berlin SIJ MRI chronic scoring**
  - *Song et al. Semin Arthritis Rheum. 2016 Feb;45(4):404-10*
  - Fatty lesions & erosions scored 0-2 per SIJ quadrant
  - Sclerosis and ankylosis scored 0-1 per SIJ (L and R)



CT – Efficacy CT Spine Score (CTSS)

- Important to use Low Dose CT (<4mSv)
- Coronal and sagittal views scored separately
- Scoring includes cervical, thoracic and lumbar spine (C2-S1)
- Syndesmophytes scored 0-3 for presence and severity



de Bruin F, *et al*. *Ann Rheum Dis* 2018;**77**:371–377. doi:10.1136/annrheumdis-2017-212553

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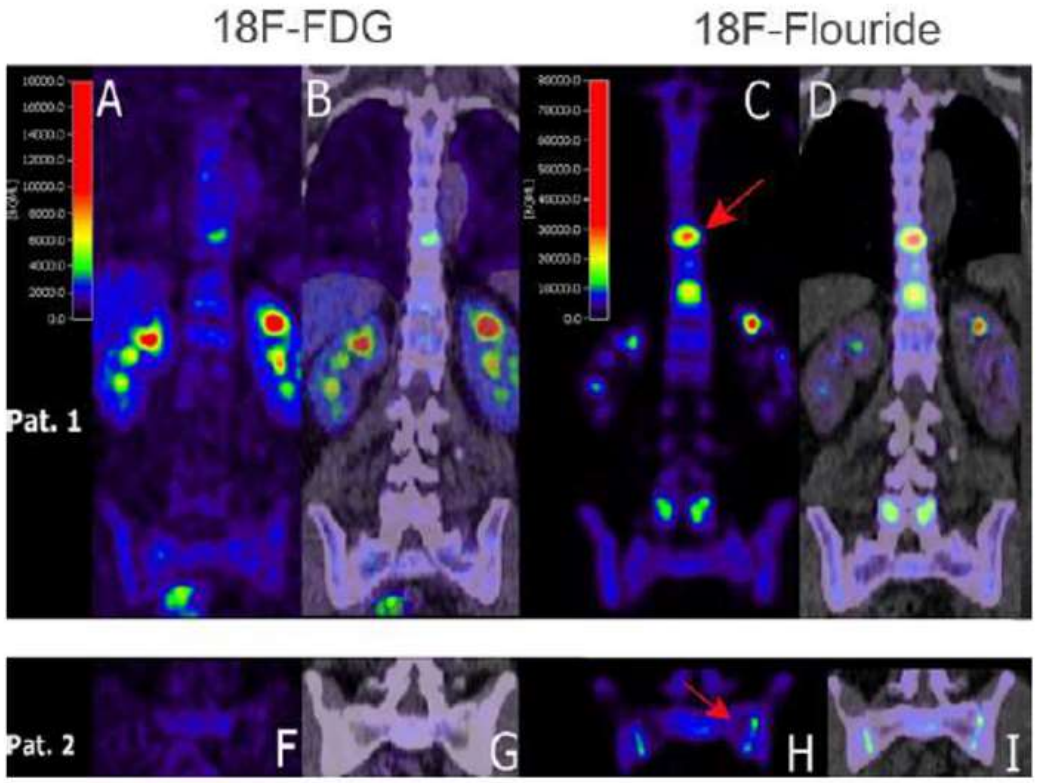
PET

- Sodium Fluoride PET scans for assessing osteoblastic activity (bone formation)
- Exploratory endpoints for bone formation and edema
- Early phase POC studies
- Quantitative SUV AUC



Bruijnen et al. Arthritis research and Therapy 2012

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Axial SpA Imaging for Clinical Trials

Challenges with Imaging in AS Studies

- High quality imaging required (artifact-free)
  - Requires careful QC with queries and rescans
- Sacro-iliac joint MRI views not standard in clinical practice
  - Lots of site training and rescans
- SPARCC spine scoring – can be difficult to select the 6 DVU's to score
- Subjectivity of assessment criteria, particularly NYmAS criteria
- Requires highly trained expert readers

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Modified New York criteria Variability: what does the literature tell us?

A seminal paper on this topic is derived from results from the French DESIR cohort authored by van den Berg et al in 2014

This paper looks at:

- Inter-reader agreement between central readers
- Reader agreement between central and local reads

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 9, September 2014, pp 2403–2411
DOI 10.1002/art.38738

Agreement Between Clinical Practice and Trained Central Reading in Reading of Sacroiliac Joints on Plain Pelvic Radiographs

Results From the DESIR Cohort

Rosaline van den Berg,[1] Grégory Lenczner,[2] Antoine Feydy,[3] Désirée van der Heijde,[1] Monique Reijnierse,[1] Alain Saraux,[4] Alain Rahmouni,[5] Maxime Dougados,[6] and Pascal Claudepierre[7]

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Main conclusions from the DESIR study

- Inter-reader agreement between the central readers was moderate (Kappa =0.54) with a 15.7% adjudication rate
- Agreement between local reading and central reading was also moderate (Kappa = 0.55);
- When local and central reads were compared based on “at least unilateral obvious sacroiliitis”
  - Local reads had a positive rate of 26.6%
  - Central reads had a positive rate of 21.1%
- A significant proportion of locally recognized ankylosing spondylitis (AS) patients were NOT CONFIRMED as having AS by central reading (false positive), while a small minority of patients were false negative
- The adjudication rate (due to inter-reader variability) is around 15%

van den Berg et al in 2014

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Site-Central Discrepancy for mNY: What have we learned recently?

Eligibility Rates in Axial Spondyloarthritis Clinical Trials Based on Imaging Criteria

Farhan A Syed, PhD, David Bennett, PhD, Michael O'Connor, PhD, Gabriele Pradella, Sarah Warner, PhD

PAREXEL International, Billerica, MA, USA

4,736 subjects from seven multi-center clinical trials were assessed for mNY +/-

Percentages of subjects deemed eligible for nr-AxSpA (mNY-) or AS (mNY+) based on central review

TYPE OF AXSPA POPULATION	RADIOGRAPHIC INCLUSION CRITERIA	TOTAL # ANALYZED	# MNY+ (%)	# MNY- (%)
AS	mNY+	2240	1180 (52.6%)	1058 (47.2%)
nr-AxSpA	mNY-	3915	1134 (29%)	2778 (70.9%)

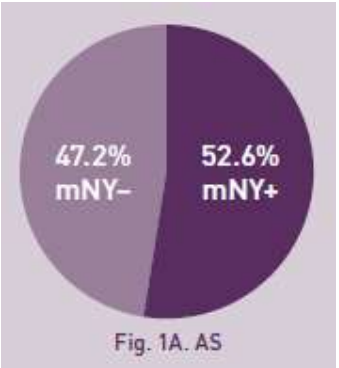

Fig. 1A. AS

Fig. 1B. nr-AxSpA

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Considerations for Clinical Trials

- Recommend implementing:
  - Early decision on assessment criteria and KOL
  - Training investigator sites on eligibility criteria
  - KOL readers for central independent review
  - Double read and adjudication for eligibility
  - Screening for both AS and nr-axial SpA at the same time
  - MRI for all subjects

Protocol Imaging Considerations

- **Imaging Modality?**
  - XR & MRI, but depends on objectives and mechanism
- **Eligibility central review or local review of images?**
  - Central read with Double read with adjudication recommended
- **Eligibility and Efficacy Imaging Assessments?**
  - Spine and SIJ, depends on the objective and mechanism of action
- **Key Opinion Leaders to involve/consult?**
  - Make decision early and they will advise use of criteria they prefer
- **Population to enroll?**
  - Efficiencies gained if both non-radiographic axial SpA and AS patients recruited & stratified

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Thank You!